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# Timing of Surgery in Rasmussen Syndrome: Is Patience a Virtue?

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Rasmussen syndrome affects previously normal people and forever changes their lives and the lives of their families. Although understood as a probable autoimmune condition, medical treatment remains limited and surgery remains the only cure, although with inevitable functional consequences. Difficulties remain in deciding on the optimal timing of surgery. Here, we review data available to aid clinicians faced with making the decision of when to recommend hemispherectomy. Not all patients have rapidly progressive disease, however, and such patients may benefit from immunomodulatory treatment. Thus, a patient's clinical course requires careful evaluation in order to identify those who would benefit most from early surgery.

Rasmussen syndrome is named after Theodore Rasmussen, who first described this condition in 1958 (1). Most patients present for clinical evaluation in the late toddler and early school-age years, but cases have been reported at younger and older ages, even adults (1). In the overwhelming majority of patients, the disease remains unihemispheric. One of the hallmarks of this condition is intractable focal epilepsy, particularly epilepsia partialis continua (EPC). Other features include unilateral hemispheric atrophy and progressive neurologic dysfunction, including both hemiparesis and cognitive decline. Rasmussen syndrome is believed to be an immune-mediated illness, but the exact pathophysiology and the role of environmental factors have not been fully delineated, despite decades of effort (2). Medical treatment has therefore been limited. Hemispherectomy remains the only cure to epilepsy, but with inevitable functional consequences of hemiparesis and hemianopia. Decisions about when surgery is appropriate are often difficult. It will be suggested where there is high risk of cognitive decline from disease, but difficulties arise in decision making when any degree of language transfer is unclear. On weighing the pros and cons about surgery, one problem is that most studies of Rasmussen syndrome have involved small numbers of patients with varying degrees of pathology. In surgical series, patients with Rasmussen syndrome frequently are mixed with patients who have had surgery for other pathologies. Thus, data supporting a recommendation for early versus late surgery in Rasmussen syndrome are sparse.

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## Natural History

Before discussing interventions, it is important first to understand the natural history of Rasmussen syndrome. This can be a progressive disease in terms of overall functional decline (3). Decline can occur with respect to seizures, hemiparesis, development, and cognition. Anatomic changes can include cortical atrophy on MRI, evidenced by a decline in hemispheric ratio, a radiographically derived measure of hemispheric symmetry, over time (4). Classic descriptions of Rasmussen syndrome suggest that patients progress to a certain maximum level of neurologic deficits, and then their illness appears to plateau at an end stage, or "burn out." However, it appears not all patients progress to severe deficits (5). Conversely, not all "burn out," patients and their deficits may continue to progress. The main argument for discussing aggressive treatment has been the probable impact of ongoing seizures on overall cognitive performance, and the perception that although a unilateral disease, there is a degree of epileptic encephalopathy affecting the normal contralateral hemisphere. Longitudinal assessment of a series of patients has demonstrated that this is not inevitable, and therefore careful astute serial clinical observations are required to determine those at risk. Interictal EEG may be helpful in this respect in that significant cognitive decline appears to be related to the appearance of independent contralateral interictal epileptiform activity, and this may therefore be a marker of who requires major intervention (5).

## Treatment

### *Medical Treatment*

The two goals of treatment are alleviation of seizures and cessation of progressive neurologic deficits. There are a number of anticonvulsants used to treat the seizures in Rasmussen syndrome, but none yield seizure freedom; EPC is particularly resistant to antiepileptic drug (AED) treatment. On the as-

**TABLE 1.** ***Immunomodulators Used in Rasmussen Syndrome***

| |
|---|
| • Corticosteroids |
| • Intravenous immunoglobulin |
| • Plasma exchange |
| • Tacrolimus |
| • Rituximab |
| • Cyclophosphamide |

sumption that there is an underlying autoimmune process, immunomodulators have been used in an attempt to control this (Table 1) (1, 4, 6–11; E. P. G. Vining, personal communication). Case series suggest these agents may be effective in slowing down a progressive course. One concern is whether immunomodulators slow down an immune-mediated process but as a consequence delay the need for more definitive treatment and thus cause an important period of neuroplasticity, required for successful rehabilitation, to be missed.

***Surgical Treatment***

Hemidisconnection is the only management option that achieves seizure freedom (1). For reasons that are unclear, partial resections that incompletely disconnect and resect abnormal tissue provide only temporary relief and require reoperation even in the presence of apparently clearly focal disease. Hemidisconnection provides a 63 to 85 percent seizure-freedom rate (1). Complication rates range from 24 to 41 percent, depending on the definition (12–14). Another potential benefit from surgery is that it frequently decreases medication burden and resulting side effects. There are however inevitable neurologic sequelae. Hemiplegia results in problems with gait (walking is usually reestablished after rehabilitation) and an inability to perform fine fractionated finger movements (which remain a challenge for patients). Hemianopia typically is compensated with minimal rehabilitation effort. Behavior may need to be addressed in some patients. Language function is an ongoing concern for patients with dominant hemisphere resections (1), returning to a variable degree. Because of these deficits, patients typically undergo aggressive rehabilitation after surgery. Therefore, overall success of hemispherectomy is related in part to the rehabilitation process.

**Rehabilitation**

Rehabilitation for patients after hemispherectomy includes physical therapy for gait and balance, occupational therapy for hand function and activities of daily living, speech/language pathology, neuropsychology for cognitive function, and sometimes, treatment for behavior difficulties. Evidence for each major area after hemispherectomy will be discussed in turn.

***Sensorimotor Function***

In patients with Rasmussen syndrome, there is some suggestion that earlier age at surgery is associated with improved sensorimotor function compared with children who undergo surgery at a later age. In a recent study of children who underwent hemispherectomy for differing etiologies, motor function (assessed by Flugl–Meyer scores) was better in those with younger age at time of surgery, as was the great toe vibration threshold (a measure of sensory function) in the paretic foot (15). This study included only a small number of patients with Rasmussen syndrome, and it is therefore unclear whether the interval between diagnosis and surgery (and thus, the timing of surgery) was a major factor. Nonetheless, it outlined measures that can be followed in future studies.

***Language Function***

One case series of four right-handed patients after right hemispherectomy for Rasmussen syndrome found that improvements in social language and communication were related to shorter duration of epilepsy and earlier age of onset (16). In this small series, one potential confounder in the study was the extent of pathology, in that it was unclear whether outcomes were worse in patients with more diseased cortex than in those with only minimal pathology.

One particularly concerning population comprises children and adolescents who require a resection of the language-dominant hemisphere. The main question is whether remaining structures can reliably assume language function. Further, one major question that consistently remains unanswered is whether relocalization should be forced by early surgery, or the disease process be allowed to progress for natural relocalization in the first instance. One series studied six right-handed children with left-hemisphere Rasmussen syndrome after a left hemidecortication (17). All had normal language for 5 years prior to seizure onset. One year after surgery, the only expressive language in all patients was single words, suggesting that late dominant-hemisphere resections lead to suboptimal language outcomes. In a larger series from the same institution, patients with left-sided disease had worse outcomes with respect to general intelligence, receptive language, and expressive language (18).

However, not all patients with dominant-hemisphere disease have poor outcomes. One case report demonstrated new activation of right-sided structures on fMRI after hemispherectomy, demonstrating radiographically that language function can transfer to the contralateral hemisphere in some cases, while other case reports have documented varying findings on late recovery of language function after hemispherectomy (19–25). The question that arises from these data is whether hemispherectomy is best performed at a younger age while remaining structures still have a fair amount of neuroplasticity or should surgery be delayed until function may, or may not, have been established in tissue that would remain connected after a hemispherectomy? We do not have the means to predict who will recover language function postoperatively, but in older children we are able to track possible change in localization over time with fMRI.

***Developmental Outcomes***

The premise for early surgery in many cases is the presumed catastrophic effect epilepsy has on the contralateral normal hemisphere, a presumed epileptic encephalopathy. In one large hemispherectomy series, seizure duration was inversely correlated with developmental quotient, arguing for early surgery (26). The subset of patients with Rasmussen syn-

drome showed a small increase in developmental quotient after surgery. Another series examined 16 hemispherectomy patients, 9 of whom had Rasmussen syndrome, and found that a shorter interval to surgery predicted improved mental and social age (27). However, as outlined above, in children followed longitudinally, not all children show a drop in intellectual ability over time, and it is difficult to know whether these surgical series have considered the neuropsychological evaluation in the decision-making process (i.e., are only individuals who are at risk of decline included?). In a series of 16 children followed longitudinally, only 7 showed a significant decline in (>15) IQ points. This appeared to be associated with the appearance of contralateral-independent interictal epileptiform activity (5). Cognitive decline is therefore not inevitable; contralateral interictal epileptiform activity may highlight those at risk.

***Adaptive Function***

In a case series of 24 children after hemispherectomy (four of whom had Rasmussen syndrome), shorter duration of epilepsy predicted good adaptive function (13). Younger age at surgery and etiology only predicted subscores, not overall scores. Age at onset of epilepsy did not predict good adaptive function.

**Decision Making With Regard to Timing of Surgery**

In children with either catastrophic onset of Rasmussen syndrome, with rapid development of EPC and hemiparesis, not responding to medical treatment, especially in nondominant disease, a decision to proceed to surgery may appear relatively "easy." Similarly, patients with a fairly mild course with intermittent seizures and no evidence of neurologic deficit can be treated medically with careful monitoring. The difficulty in decision making, however, arises in those falling between these extremes. Those with a progressive but not rapidly deteriorating course, particularly where there is evidence that the disease process involves the dominant hemisphere, present a significant challenge. After all, seizures may continue and possibly worsen. Aside from any discussion of the impact of recurrent seizures on the brain, there is concern for injury, including falls and their sequelae. There are also the adverse effects of medication, including metabolic problems, sedation, cognitive and language effects, immunosuppression, and the consequence of corticosteroids. Language rehabilitation depends on the ability of the contralateral hemisphere to assume new function. Finally, hemiplegia also has an impact on mobility and the activities of daily living. Thus, progressive disease can lead to significant consequences. Hemidisconnection, however, also has an inevitable functional consequence.

What if surgery is delayed? Not all children respond to immunomodulatory therapy. In these children also, in view of seizure severity, a decision to proceed to surgery may be made earlier rather than later. However, some do show a clinical response to medical treatment. In a series reported, there is slowed progression of the hemiparesis and hemiatrophy on MRI compared with historical controls (5; Varadkar et al., personal communication). What is unknown is the consequence on longer term functional outcome from waiting or the impact on transfer of language. Any transfer of language into the previously nondominant hemisphere can be assessed with fMRI in cooperative children. Consequently, a more accurate prediction of likely postoperative language function can be made. Group data suggest preoperative neuropsychological scoring will determine postoperative scores (18), and consequently better outcome may be assumed from surgery earlier in the natural history of the disease. We have little evidence however that all children should undergo hemidisconnection at diagnosis. Each case has to be monitored carefully and decisions made on an individual basis. Inevitably, it follows that all such children should be followed in centers experienced in medical and surgical management of this condition.

**Conclusions**

The decision about when to perform hemispherectomy in Rasmussen syndrome is one of the most difficult that a patient, family, and physician will ever have to make. Patients with mild deficits that do not appear to be progressing rapidly are good candidates for immunotherapy. Similarly, those with very rapid progression of seizures and symptoms are best treated with hemispherectomy early in their natural history. The most challenging and largest group includes those patients whose course is moderately progressive and/or fluctuating. These patients may benefit from trials of immunomodulators but need to be evaluated carefully from a developmental and cognitive perspective in order to optimize timing of hemidisconnection. Future investigations need to include prospective series from multicenter collaborations in order to increase the power of findings and more rigorously identify subsets of patients who need surgery sooner rather than later.

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